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The effect of menopause on objective sleep parameters: Data from an epidemiologic study in São Paulo, Brazil

Helena Hachul[a,b,c,*], Cristina Frange[a], Andréia Gomes Bezerra[a], Camila Hirotsu[a], Gabriel Natan Pires[a], Monica Levy Andersen[a], Lia Bittencourt[a], Sergio Tufik[a]

[a] Departamento of Psicobiologia, Universidade Federal de São Paulo (UNIFESP), São Paulo, SP, Brazil
[b] Departamento de Ginecologia, Universidade Federal de São Paulo (UNIFESP), São Paulo, SP Brazil
[c] Departamento de Ginecologia, Casa de Saúde Santa Marcelina, São Paulo, SP, Brazil

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ABSTRACT

Objective: Our objective was to investigate the influence of menopausal status on sleep patterns in a representative sample of women from São Paulo, Brazil.
Study design: A population-based survey with a probabilistic three-stage cluster sample of the city of São Paulo was used to represent the local population according to gender, age (20–80 years) and socioeconomic status.
Main outcome measures: The female participants answered a sleep questionnaire, underwent polysomnographic recording and allowed their hormone levels to be measured. They also completed a gynecological questionnaire for classification of the reproductive aging stages: premenopausal or reproductive, perimenopausal or menopausal transition, and postmenopausal, defined as being after 12 months of amenorrhea. Women were allocated into early (the first 5 years after menopause) and late (after the first 5 years) stages.
Results: A total of 535 women were included in this study: 339 were premenopausal, 53 were early postmenopausal, 118 were late postmenopausal and 25 were using hormone therapy or isoflavone compounds. Our main findings were that women in postmenopause spent more time in N3 sleep, had a higher apnea-hypopnea index (AHI) and lower SaO_2 compared with premenopausal women after an analysis adjusted for confounding factors. We found no significant differences between early and late postmenopausal women in the adjusted analysis.
Conclusion: Our results indicate menopause itself exerts a modest, but important influence on objective sleep patterns, independent of age, in particular on AHI and SaO_2.

1. Introduction

Sleep is a complex phenomenon of physiologic and behavioral processes, necessary to maintain quality of life at any age. Sleep is classified into rapid eye movement (REM) sleep and non-REM (NREM) sleep, the latter being further subdivided into Stage 1 (N1), Stage 2 (N2) and Stage 3 (N3). Stage 3 is also known as slow wave sleep (SWS) or deep sleep [1]. In normal individuals, NREM sleep predominates in the first half of the night, while REM sleep is more frequent in the second half of the night (Fig. 1).

Sleep can be measured subjectively and sleep pattern, objectively through polysomnography (PSG). Some of its variables are: Sleep Latency (time it takes to fall asleep: normally under 30 min), Total Sleep Time (TST) (variable within person), Sleep Efficiency (greater than 85% of TST), Stages N1 (up to 5% of TST), N2 (45–55% of TST), N3 or SWS (up to 23% of TST), REM sleep (20–25% of TST) and apnea hypopnea index (AHI) (normal index is under 5 events per hour and defined as the mean number of obstructive apneas and hypopneas per hour of sleep) [2].

Sleep alterations are associated with the aging process [3] as sleep complaints become more frequent at older ages [4]. Sleep patterns change across lifespan in both genders. For adults, sleep latency, stage N1 (light sleep) and the amount of time spent awake after sleep onset (WASO) significantly increase with age, while TST and SWS decrease with age [5]. Sleep efficiency also declines with age [6].

Sleep disturbance is a common complaint of middle-aged women and is often attributed to the transition to menopause [7,8].

* Corresponding author at: Universidade Federal de São Paulo, Departamento de Psicobiologia, Napoleao de Barros 925, 04024-002 Sao Paulo, SP, Brazil.
Tel.: +55 11 2149 0155; fax: +55 11 5572 5092.
E-mail address: helena.hachul@hotmail.com (H. Hachul).

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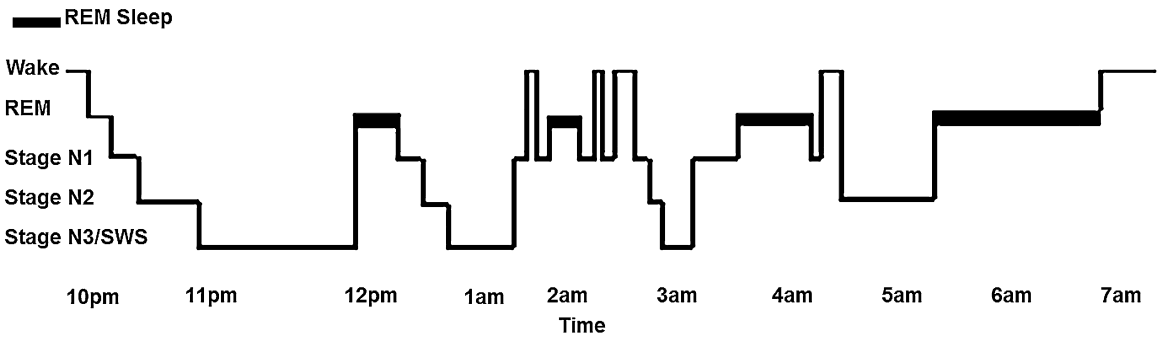

Fig. 1. *Hypnogram of a normal night's sleep.* REM sleep: rapid eyes movement; stage 1 (N1); stage 2 (N2); stage 3 (N3 or SWS: slow wave sleep), also known as deep sleep

Menopausal status, age and depressed mood are factors associated with sleep disturbance [9].

More recently, sleep has been investigated in the female population, with some evidence showing the impact of hormones on sleep during the different phases of women's lives [10,11]. Thus, menopause is considered an important stage in women's lives as evidence points to an increase in sleep problems (evident in midlife), as well as an increase in other diseases/comorbidities, pain, mood symptoms and weight gain [12].

Sleep difficulties can be initiated by menopause transition and there are factors that are often observed during the same period, as the effect of hormone therapy on sleep, sleep-disordered breathing, pain disorders, movement disorders and comorbidities [12]. Sleep disturbances may increase during menopausal stages, becoming severe in postmenopause [13], and leading to a higher risk of having poor subjective sleep quality and quantity [14] as well as an increased AHI [15]. Also, there is some evidence of the effect of menopause on sleep. Women in perimenopausal and postmenopausal stages have an increased risk of having sleep problems, compared to premenopause [16,17]. Within the menopausal transition, perimenopausal women may have longer and more frequent periods of arousal with an increased prevalence of mood symptoms compared to postmenopausal women [18]. In addition, postmenopausal women have shorter sleep duration, report more insomnia and use more sleep medications than premenopausal women [19].

In a study controlled for age with a large sample size, the odds ratio for sleep problems in postmenopausal women was 1.5 compared to premenopausal [20]. Postmenopausal women were also 1.5 times more likely to have an AHI greater than 5 relative to premenopausal women and indeed presented lower sleep efficiency and REM sleep, and more sleep alterations due to menopause status [15].

Few studies have focused directly on the association of menopause stages on sleep using objective methods such as PSG and considering the influence of age in an epidemiological sample [21–25]. Large population-representative surveys worldwide would provide important information about the prevalence of specific symptoms and problems in women and their associations with quality of life. Thus, this study aimed to explore the association of menopausal stages (premenopausal *versus* postmenopausal) and of postmenopausal stages (early *versus* late) with sleep parameters in a representative sample of women from the city of São Paulo, Brazil.

2. Methods

2.1. Study design

This study is a part of a cross-sectional study called the São Paulo Epidemiologic Sleep Study (EPISONO), conducted in São Paulo (Brazil) in 2007. It is a population-based survey, with a probabilistic 3-stage cluster sample from the city of São Paulo, weighted to match the demographic projections for the city inhabitants in 2007 by gender, age and socioeconomic status. These projections were derived from the 2000 city census.

2.2. Sampling procedures

An initial sample size of 1056 participants from both genders was defined to obtain a representative sample of the city of São Paulo, using a 3-stage cluster sampling technique [27]. In the first stage, to assure the representativeness of different levels of wealth, 96 districts (from the 1500 districts in which the city is divided for census purposes) were proportionally selected from the 4 homogenous socioeconomic macro-regions of São Paulo. Slums and shantytowns were excluded due to high criminal activity, as they were considered risk areas for the safety of the interviewers involved in the current study. Households were selected if they were permanently occupied private homes, thus clinics, schools, and other commercial and non-commercial establishments were excluded. In the second stage, the selection of a given household was made by randomly picking the first home and subsequently skipping a specified number, calculated by dividing the total number of homes by a fixed number, to select 11 households in each sector. Each apartment in an apartment building was considered a home, and counting was carried out from the upper floor to the lower floor. Finally, in the third stage of sampling, all eligible residents of each chosen home were ranged from the youngest to the oldest, and the subject was selected by means of 96 pre-established random tables, which designated which individual to choose from each of the 11 households, from the 96 selected districts.

Pregnant and lactating women, people with physical or mental impairments that prevent self-care, individuals below 20 or over 80 years old and people who work every night were not included in the selection from the household. Substitutes were chosen from the next home, following the same random selection criteria described above. In addition, individuals were not included in the following instances: following 3 unsuccessful attempts to contact the target individual, total refusal to participate, obstruction by a family member, or inability to participate for a specified reason [26]. These individuals were replaced using method described above.

2.3. Subjects

From the total of 1056 who agreed to participate in the study, 1042 completed the study. Of those, 574 were women and were included in the current study. Thus, all the female population of the EPISONO was considered for this study. At the time of selection, all participants signed a written consent that was included in the sleep questionnaire, which authorized us to collect and use data for future research studies. The volunteers that agreed to visit the Sleep Institute were collected by car on the scheduled visit date

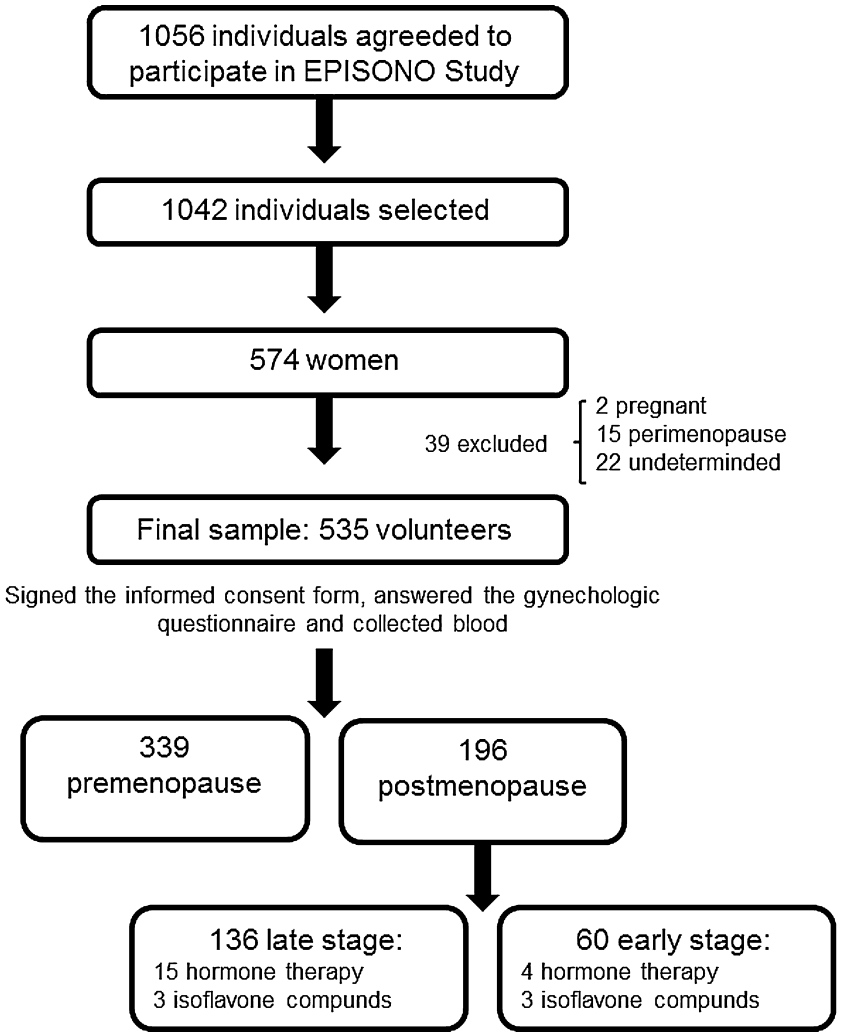

Fig. 2. Enrollment schema used in the current protocol design for this study.

from a place of their choice about 2 h before their usual bedtime. The study protocol was approved by the University Ethics Committee (CEP 0593/06) and registered with ClinicalTrials.gov (Identifier NCT00596713).

2.4. Clinical diagnostic

In respect of gynecological status, the subjects included in this study were grouped into the following menopausal stages: premenopausal or reproductive, perimenopausal or menopausal transition and postmenopausal [28]. This classification was based on both: their responses to the gynecological questionnaire, which included questions about menstrual cycles, premenstrual complaints, use of hormonal contraceptives, dysmenorrhea, menopause, hot flashes and hormonal therapy; and on hormone measurements, evaluated on the morning after polysomnography. Premenopausal or reproductive status was defined as having an ongoing menstrual cycle. A regular menstrual cycle was defined as menses with a cycle that spans 25–35 days. Postmenopausal women were defined by amenorrhea for at least 1 year before enrollment and confirmed using hormonal levels of FSH and LH concentrations of more than 30 mIU/mL. Postmenopause was further distributed into 2 stages: early and late. The early stage encompasses the first 5 years after menopause and the late stage includes the period after that, in line with the criteria of the stages of reproductive aging workshop (STRAW) [28].

The women filled out a questionnaire (Women's Questionnaire for the São Paulo Sleep Institute) which included 19 questions about menstrual cycles and was used to classify them into menopausal stages. Also, the presence of hot flashes (Yes or No) was assessed.

2.5. Groups

Fig. 2 depicts the steps of the enrollment schema used in the current protocol design for this study.

For comparison between early and late postmenopause, women using hormonal therapy were also excluded from the analysis. Due to missing data (8 missing for neck circumference, 10 missing for waist circumference, 11 missing for hip circumference, 9 missing for systolic blood pressure, 9 missing for diastolic blood pressure, 9 missing for REM sleep and 1 missing for basal SaO_2), the final *N* was different for some of the parameters analyzed.

2.6. Physical measurements

General physical measurements were made before the PSG was performed and included body weight (kg) and height (m), which were used to calculate body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters), and systolic and diastolic blood pressure (mmHg).

Table 1
Comparison of data between premenopausal and postmenopausal women and between early and late postmenopausal women.

	Premenopausal ($n = 339$)		Postmenopausal						*P* values	
			Total ($n = 196$)		Early ($n = 53$)		Late ($n = 118$)			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Pre × post	Early × late
Age (years)	34.6	8.4	59.5	9.3	52.2	5.3	63.3	8.6	<0.001	<0.001
BMI (kg/m^2)	25.8	5.4	28.8	5.6	28.8	5.1	29.1	6.2	<0.001	NS
Neck circunference (cm) [a,d]	33.2	2.6	34.6	2.6	34.3	2.6	34.7	2.7	<0.001	NS
Waist circunference (cm) [b,e]	79.1	11.7	88.8	13.4	88.9	11.6	89.5	14.4	<0.001	NS
Hip circunference (cm) [a,d]	100.3	13.8	104.6	12.8	104.6	14.0	105.4	12.5	<0.001	NS
Systolic blood pressure (mmHg) [c,f]	118.1	18.7	139.0	23.5	131.1	22.5	142.7	23.7	<0.001	<0.01
Diastolic blood pressure (mmHg) [c,f]	77.2	12.2	84.2	12.3	81.6	10.5	85.2	11.6	<0.001	NS

SD: standard deviation; BMI: body mass index calculated based on the body weight and height during the study. Sample size varied among comparison due to missing values, as follows:

[a] Premenopause $n = 335$, postmenopause $n = 192$.
[b] Premenopause $n = 334$, postmenopause $n = 191$.
[c] Premenopause $n = 335$, postmenopause $n = 191$.
[d] Early postmenopause $n = 52$, late post menopause $n = 116$.
[e] Early postmenopause $n = 51$, late post menopause $n = 116$.
[f] Early postmenopause $n = 52$, late post menopause $n = 115$. *P* values obtained through Student's *t*-test.

2.7. Hormonal measures

In the morning after PSG recording, blood was drawn from a peripheral forearm vein to evaluate fasting hormone levels after an overnight fast of 12 h. The blood was collected in appropriate tubes according to the required laboratory tests. LH, FSH and 17β-estradiol were measured using the acrinidin-ester chemiluminescence method (Advia Centaur; Siemens Healthcare Diagnostics Inc, Tarrytown, New York, USA) and were used to distribute the women into groups according to menopausal status, as described above.

2.8. Polysomnography

All PSG tests were done at the Sleep Institute (São Paulo, Brazil), a sleep laboratory with 80 beds (www.sono.org.br), always respecting the usual time the participants went to bed. All of the participants completed the UNIFESP Sleep Questionnaire to determine their sleep schedules during working and non-working days at the time of the home selection [29]. Participants were asked about their sleep routines and wake-up times during the week, at weekends and on holidays. The PSG was scheduled according to the availability of the volunteers, and most of them were performed during weekdays (64%). The scheduling of PSG did not take into consideration the menstrual cycle, only the availability of the participants.

Participants underwent a full-night of PSG, which was performed using a digital system (EMBLA® S7000, Embla Systems Inc., Broomfield, CO, USA) during their usual sleep time. The following physiological tests were performed: electroencephalography (EEG, C3–A2, C4–A1, O1–A2, O2–A1), electrooculography (EOG, EOG-left-A2, EOG-right-A1), electromyography (EMG, muscle of the submentonian region, tibialis anterior muscle, masseter region, and 17th intercostal space), electrocardiography (ECG, derivation V1 modified), and airflow detection by a thermocouple and by nasal pressure. In addition, the following physiological parameters were evaluated: respiratory effort using thoracic and abdominal *x*-trace belts, snoring and body position by EMBLA sensors, and arterial oxygen saturation (SaO_2) and pulse rate by an EMBLA oximeter. All PSG were visually scored by a registered and trained PSG technologist, who was blind to the menstrual cycle of women. All sleep stages were scored according to standardized criteria

Table 2
Comparison of objective sleep patterns between premenopausal and postmenopausal women in unadjusted analysis in EPISONO.

	Premenopausal ($n = 339$)			Postmenopausal ($n = 196$)			*P* value
	Mean	SD	95% CI	Mean	SD	95% CI	
Sleep latency (min)	15.3	18.8	12.9–17.7	20.5	28.7	17.3–23.7	<0.05
REM sleep latency (min)[a]	99.6	47.8	93.7–105.5	115.8	65.5	108.0–123–6	<0.01
Total sleep time (min)	351.1	79.1	342.9–359.4	318.1	74.2	307.2–329.0	<0.001
Sleep efficicency (%)	84.2	12.7	82.8–85.6	77.2	13.9	75.4–79.1	<0.001
Stage N1 (%)	4.0	3.2	3.6–4.3	5.0	3.3	4.5–5.5	NS
Stage N2 (%)	54.5	8.0	53.5–55.4	54.9	10.8	53.6–56.1	NS
Stage N3 (%)	22.3	7.5	21.4–23.2	23.0	9.3	21.8–24.2	NS
REM sleep (%)	19.2	6.6	18.5–19.9	17.1	6.7	16.2–18.1	<0.001
Arousal index (number/h)	10.6	6.2	9.7–11.5	17.1	11.6	15.9–18.3	<0.001
Microarousal (number)	45.7	38.6	40.6–50.8	57.1	60.8	50.4–63.9	<0.05
WASO (min)	50.6	44.7	45.7–55.5	74.8	47.2	68.4–81.2	<0.001
PLM index (PLM/h)	0.7	7.4	0.0–1.5	1.8	6.8	0.8–2.8	NS
AHI (number/h)	2.0	4.0	0.9–3.2	13.0	16.4	11.6–14.5	<0.001
Basal SaO_2 (%)[a]	96.9	1.1	96.8–97.1	95.0	1.7	94.8–95.1	<0.001
Mean SaO_2 (%)	96.3	1.2	96.2–96.5	93.9	2.0	93.7–94.1	<0.001
Minimum SaO_2 (%)	91.6	3.5	91.1–92.1	84.6	6.2	83.9–85.2	<0.001

SD: standard deviation; CI: confidence interval; NS: not significant; REM: rapid eye movement; WASO: wake after sleep onset; PLM: periodic leg movements index (number/h); AHI: apnea-hypopnea index (number/h); SaO_2: oxygen saturation level.

[a] Exception on sample size, due to missing date: REM sleep latency: premenopausal $n = 335$ and postmenopausal $n = 191$; basal SaO_2(%): premenopausal $n = 338$ and postmenopausal $n = 196$. *P* values acquired through Student's *t*-test.

Table 3A
Comparison of objective sleep patterns between premenopausal and postmenopausal women in adjusted analysis for age, body mass index, systolic blood pressure, diastolic blood pressure, neck, waist and hip circumference in EPISONO.

	Premenopausal ($n = 339$)			Postmenopausal ($n = 196$)			*P* value
	Mean	SD	95% CI	Mean	SD	95% CI	
Sleep latency (min)	16.8	24.1	14.3–19.4	14.3	28.4	10.3–18.3	NS
REM sleep latency (min)[a]	100.7	70.3	93.2–108.2	110.3	82.2	98.6–121.9	NS
Total sleep time (min)	335.2	93.5	325.2–345.2	355.8	110.2	340.4–371.3	NS
Sleep efficicency (%)	81.4	14.6	79.8–82.9	84.5	17.2	82.0–86.9	NS
Stage N1 (%)	4.1	4.0	3.7–4.6	4.3	4.7	3.7–5.0	NS
Stage N2 (%)	55.1	11.7	53.8–56.3	53.3	13.8	51.3–55.2	NS
Stage N3 (%)	21.3	10.5	20.2–22.4	24.5	12.3	22.8–26.3	<0.05
REM sleep (%)	19.4	8.3	18.5–20.3	17.9	9.8	16.5–19.3	NS
Arousal index (number/h)	12.5	10.2	11.5–13.6	12.8	12.1	11.1–14.5	NS
Microarousal (number)	51.3	62.3	44.7–58.0	48.8	73.4	38.5–59.1	NS
WASO (min)	60.1	54.0	54.4–65.9	52.3	63.6	43.3–61.2	NS
PLM index (PLM/h)	1.6	8.9	0.6–2.5	0.5	10.5	−1.0–1.9	NS
AHI (number/h)	4.1	12.6	2.8–5.5	8.6	14.8	6.5–10.7	<0.01
Basal SaO_2 (%)[a]	96.5	1.5	96.3–96.6	95.8	1.8	95.5–96.0	<0.001
Mean SaO_2 (%)	95.8	1.8	95.6–96.0	94.9	2.1	94.6–95.2	<0.001
Minimum SaO_2 (%)	90.5	5.6	89.9–91.1	86.6	6.6	85.7–87.5	<0.001

SD: standard deviation; CI: confidence interval; NS: not significant; REM: rapid eye movement; WASO: wake after sleep onset; PLM: periodic leg movements index (number/h); AHI: apnea-hypopnea index (number/h); SaO_2: oxygen saturation level.

[a] Exception on sample size, due to missing date: REM sleep latency: premenopausal $n = 335$ and postmenopausal $n = 191$; basal SaO_2(%): premenopausal $n = 338$ and postmenopausal $n = 196$. *P* values acquired through ANCOVA.

for investigating sleep [2]. EEG arousals and leg movements were scored according to the criteria established by the American Academy of Sleep Medicine (AASM) Manual for Scoring Sleep and Associated Events [30]. Apneas were scored and classified following the recommended respiratory rules for adults suggested by the AASM manual and hypopneas were scored according to the alternative rules [30]. Four percent of the PSG results were randomly rescored by a registered PSG technologist to confirm that all of the PSG scoring had been executed correctly (agreement rate of $93.36 \pm 5.1\%$, $k = 0.91 \pm 0.03$).

2.9. Statistical analysis

Data analysis was performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). All of the data that did not meet the assumptions of normalization and homogeneity were transformed into *z*-score for a suitable parametric evaluation. For comparison of alcohol consumption, smoking, occupation and marital status, frequencies were analyzed using chi-square test. To compare groups defined by menopause status (premenopause *versus* postmenopause; early *versus* late postmenopause), Student's *t*-test was used. For analysis of the effect of menopause status on sleep parameters controlled only for age or for all confounding factors, analysis of covariance (ANCOVA) through General Linear Model (GLM) was applied using only age or age, body mass index (BMI), systolic blood pressure, diastolic blood pressure and neck, waist and hip circumference as covariates. For assessing the influence of hot flashes as well as interaction with menopausal stages, we also used multiple ANCOVA (MANCOVA), with menopausal stages and hot flashes presence (Yes/No) as the dependent variables and age as the covariate. Significance was defined as $P < 0.05$. Data are reported as the mean ± standard deviation (SD).

3. Results

No significant differences were observed in relation to alcohol consumption ($\chi^2 = 2.5$, df = 1, $P > 0.05$) and smoking ($\chi^2 = 2.27$, df = 1, $P > 0.05$) between the different groups. However, with regard

Table 3B
Comparison of objective sleep patterns between premenopausal and postmenopausal women in unadjusted analysis except for age in EPISONO.

	Premenopausal ($n = 339$)			Postmenopausal ($n = 196$)			*P* value
	Mean	SD	95% CI	Mean	SD	95% CI	
Sleep latency (min)	16.9	1.6	13.78–20.2	17.7	2.4	12.9–22.4	NS
REM sleep latency (min)[a]	100.6	3.9	92.93–108.3	114.0	5.9	102.4–125.7	NS
Total sleep time (min)	335.4	5.3	322.9–343.9	348.7	8.0	333.0–364.4	NS
Sleep efficicency (%)	81.0	0.9	79.2–82.7	82.8	1.3	80.1–85.4	NS
Stage N1 (%)	4.2	0.2	3.7–4.6	4.7	0.3	4.0–5.3	NS
Stage N2 (%)	55.2	0.6	53.9–56.4	53.6	0.96	51.7–55.5	NS
Stage N3 (%)	21.4	0.6	20.3–22.6	24.5	0.9	22.8–26.2	<0.05
REM sleep (%)	19.2	0.5	18.3–20.1	17.1	0.7	15.8–18.5	<0.05
Arousal index (number/h)	12.6	0.6	11.5–13.8	13.6	0.9	11.8–15.3	NS
Microarousal (number)	49.1	3.4	42.4–55.7	51.3	5.1	41.3–61.2	NS
WASO (min)	61.3	3.1	55.2–67.5	56.2	4.7	47.0–65.5	NS
PLM index (PLM/h)	1.4	0.5	0.4–2.4	0.7	0.7	−0.8–2.2	NS
AHI (number/h)	4.0	0.7	2.6–5.5	9.6	1.1	7.4–11.7	<0.001
Basal SaO_2 (%)[a]	96.5	0.1	96.3–96.7	95.7	0.1	95.4–96.0	<0.001
Mean SaO_2 (%)	95.7	0.1	95.6–96.0	94.8	0.2	94.4–95.0	<0.001
Minimum SaO_2 (%)	90.5	0.3	89.9–91.1	86.3	0.5	85.4–87.3	<0.001

SD: standard deviation; CI: confidence interval; NS: not significant; REM: rapid eye movement; WASO: wake after sleep onset; PLM: periodic leg movements index (number/h); AHI: apnea-hypopnea index (number/h); SaO_2: oxygen saturation level.

[a] Exception on sample size, due to missing date: REM sleep latency: premenopausal $n = 335$ and postmenopausal $n = 191$; basal SaO_2(%): premenopausal $n = 338$ and postmenopausal $n = 196$. *P* values acquired through ANCOVA.

to marital status, there was a significant difference ($\chi^2 = 22.2$, df = 2, $P < 0.001$), with the separated/divorced/widowed category being more frequent in the postmenopausal women compared to the premenopausal. Socioeconomic status also significantly differed between groups ($\chi^2 = 23.5$, df = 2, $P < 0.001$), with an increased proportion of middle class in the premenopausal compared to the postmenopausal women.

Postmenopausal women had significantly higher BMI, neck, waist and hip circumference, as well as systolic and diastolic blood pressure compared to premenopausal women. In addition, within the postmenopausal group, late postmenopause women had higher SBP when compared to early postmenopause women (Table 1).

The results showed a significant effect of menopause status on sleep architecture such as sleep latency (SL) (minutes) ($t = -2.3$, df = 292.7, $P < 0.05$), REM sleep latency (minutes) (REM SL) ($t = -3.0$, df = 307.2, $P < 0.01$), total sleep time (minutes) (TST) ($t = 4.8$, df = 533.0, $P < 0.001$), sleep efficiency (SE) (%) ($t = 5.9$, df = 533.0, $P < 0.001$), stage N1 (%) ($t = -3.4$, df = 533.0, $P < 0.001$), REM stage (%) ($t = 3.5$, df = 533.0, $P < 0.001$), arousal index ($t = -7.2$, df = 260.0, $P < 0.001$), number of microarousal ($t = -2.4$, df = 287.1, $P < 0.05$), wake after sleep onset (WASO) ($t = -5.9$, df = 533.0, $P < 0.001$), AHI ($t = -9.2$, df = 208.8, $P < 0.001$), basal SaO_2 (%) ($t = 14.7$, df = 285.9, $P < 0.001$), mean SaO_2 (%) ($t = 15.1$, df = 282.4, $P < 0.001$) and minimum SaO_2 (%) ($t = 14.5$, df = 266.3, $P < 0.001$). Women in postmenopause presented increased SL, REM SL, stage N1, arousal index, microarousal, WASO, AHI as well as a reduction in TST, SE, REM and basal, mean and minimum SaO_2 compared to women in the premenopausal stage (Table 2). However, after controlling the analysis for age and the other confounding factors, we found that postmenopausal women had increased stage N3 and AHI and lower basal, mean and minimum SaO_2 when compared to women in premenopausal stage (Table 3A).

When comparing objective sleep patterns between premenopausal and postmenopausal women in an analysis unadjusted except for age, the results showed that postmenopausal women had an increase of stage N3 (%) and AHI as well as a decrease in REM sleep stage (%), and basal, mean and minimum SaO_2 (%) compared to premenopausal women (Table 3B).

The unadjusted analysis within the postmenopausal group (early *versus* late) showed that women in early postmenopause had increased stage N3 (%) ($t = 2.1$, df = 169, $P < 0.05$) and lower arousal index ($t = -2.3$, df = 169, $P < 0.05$), PLM ($t = -3.1$, df = 117.4, $P < 0.05$) and AHI ($t = -2.3$, df = 131.6, $P < 0.05$) when compared to late postmenopause women (Table 4). No significant differences were found when the analysis was controlled for the confounding factors (Table 5).

We found that from the 240 women in the premenopausal stage, 31 (12.9%) presented hot flashes, while from the total of 186 women in the postmenopausal stage, 79 (42.5%) presented hot flashes. A significant association between the presence of hot flashes and the postmenopausal stage was observed ($\chi^2 = 47.8$, df = 1, $P < 0.001$), with more women in the postmenopausal stage with hot flashes in comparison with those from the premenopausal stage.

Within the postmenopausal stage (excluding 25 women in hormonal therapy, final $n = 161$), we found that from the 52 women in the early postmenopausal stage, 25 (48.1%) presented hot flashes, while from the total of 109 women in the late postmenopausal stage, 39 (35.8%) presented hot flashes. No association was found in this case between the postmenopausal stage and the presence of hot flashes. No interaction between postmenopausal stage and hot flashes were found. The presence of hot flashes was observed only in sleep latency, as women with hot flashes had increased sleep latency.

As our study design was focused on an epidemiological sample, our aim was to take advantage of the big sample size to assess the population profile with the possibility to adjust for confounder variables such as age as well as to evaluate possible risk factors. From 30 to 60 years of age, there were women in premenopausal and in postmenopausal stages. Below 30 years of age there were only premenopausal women and above 60 years, only postmenopausal women. We also observed that within the 40–50 age group there was a balanced number of women in the premenopausal ($n = 96$) and postmenopausal stage ($n = 34$).

As sleep disturbance seems to be worse in the early years after menopause, we compared sleep parameters between premenopausal women and early postmenopausal women. We found that women in the age group of 40–50 years were not different for age and BMI, but importantly they differed in several sleep parameters, such as N2 and N3 sleep stages (%) as well as AHI, basal, mean and minimum SaO_2 (%). Postmenopausal women in the 40–50 years group presented decreases in N2 stage (%) and basal, mean and minimum SaO_2 (%), and increases in N3 stage (%) and AHI.

4. Discussion

We have presented data on a representative sample of women from São Paulo, Brazil, using PSG to show that menopause and sleep parameters are associated. PSG is the gold standard technique used for the diagnosis of sleep disorders. After taking into account differences in sleep patterns due to age, we hypothesized that menopause itself, as well as its stages (early and late postmenopause) could be negatively associated with sleep parameters.

In our study premenopausal and postmenopausal women had differences in age, BMI, systolic and diastolic blood pressure as in the study of Hung et al. [14]. Postmenopausal women experienced significantly worse sleep quality than premenopausal women in an unadjusted analysis of 12 parameters. However, when the confounders were controlled, only 5 parameters remained statistically significant: stage N3 (%), AHI and basal, mean and minimum SaO_2 (%). When comparing objective sleep patterns between premenopausal and postmenopausal women in an analysis unadjusted except for age, the results showed that postmenopausal women had an increase of N3 (%) stage and AHI as well as a decrease in REM (%) stage.

Our findings are in agreement with a previous study from our group [15] which compared pre- and postmenopausal women in a different sample, as we also found that postmenopausal women had more SWS and a greater chance of having an AHI ≥ 5 events per hour. Interestingly, this previous study found decreased stage N2 (%) and REM sleep (%), the latter also being found in the unadjusted analysis in the current study.

Contrary to these findings, menopause was not associated with diminished sleep quality in a polysomnography study from Young et al. [21], which found no differences between groups, despite postmenopausal women being less satisfied with their sleep.

Several studies have reported different normal means for N3 sleep stage in women: 10% [31], 13% [21,32], 14% [33], 23% [34,35]. We observed that the premenopausal women in this study spent 21.3% of their total sleep time in N3 (%) compared with postmenopausal women, who spent 24.5% of their total sleep time in the same stage. This indicates that a change in the amount of time spent in SWS (%) occurs, but although there is a statistical difference between groups, it is not of great clinical relevance. In fact, aging is associated with a decrease in SWS (%) [5] and this fact was not observed in our study. As in our study, Young et al. [21] also found that postmenopausal women had more deep sleep relative to premenopausal women.

Sleep problems can be caused by sleep-disordered breathing. We observed increased AHI with a consequent reduction in SaO_2 (%) in postmenopausal compared to premenopausal women.

Table 4
Comparison of objective sleep patterns between early and late postmenopausal women in unadjusted analysis in EPISONO.

	Early ($n = 53$)			Late ($n = 118$)			*P* value
	Mean	SD	95% CI	Mean	SD	95% CI	
Sleep latency (min)	17.8	21.2	11.3–24.2	20.4	24.9	16.0–24.7	NS
REM sleep latency (min)[a]	25.4	72.9	107.5–143.4	112.3	61.8	100.3–124.4	NS
Total sleep time (min)	327.6	66.9	307.9–347.3	317.0	75.0	303.8–330.2	NS
Sleep efficicency (%)	79.8	12.3	76.1–83.4	76.1	14.0	73.6–78.5	NS
Stage N1 (%)	4.7	3.6	3.8–5.6	5.0	3.3	4.4–5.6	NS
Stage N2 (%)	52.9	9.8	50.0–55.9	56.1	11.2	54.1–58.1	NS
Stage N3 (%)	24.9	8.9	22.4–27.4	21.7	9.4	20.0–23.4	<0.05
REM sleep (%)	17.4	6.3	15.6–19.2	17.2	6.8	16.0–18.4	NS
Arousal index (number/h)	14.2	10.0	11.1–17.4	18.6	12.3	16.4–20.7	<0.05
Microarousal (number)	50.1	51.1	33.6–66.6	63.5	64.5	52.4–74.5	NS
WASO (min)	67.0	44.1	53.9–80.0	80.7	49.9	71.9–89.4	NS
PLM index (PLM/h)	0.0	0.2	−1.6–1.7	2.2	7.4	1.1–3.3	<0.01
AHI (number/h)	9.5	12.8	5.1–13.8	14.8	17.2	11.9–17.7	<0.05
Basal SaO_2 (%)	95.2	1.8	94.8–95.7	94.7	1.6	94.4–95.0	NS
Mean SaO_2 (%)	94.1	2.1	93.6–94.7	93.7	2.0	93.3–94.1	NS
Minimum SaO_2 (%)	85.4	5.9	83.7–87.2	83.7	6.5	82.5–84.8	NS

SD: standard deviation; CI: confidence interval; NS: not significant; REM: rapid eye movement; WASO: wake after sleep onset; PLM: periodic leg movements index (number/h); AHI: apnea-hypopnea index (number/h); SaO_2: oxygen saturation level.

[a] Exception on sample size, due to missing date: REM sleep latency: early postmenopause $n = 52$ and late postmenopause $n = 115$. *P* values acquired through Student's *t*-test.

Two other large studies provided strong support for the hypothesis that menopause increases the risk for SDB. Bixler et al. [36] found a higher prevalence of SDB in postmenopausal compared with premenopausal women. The prevalence of an AHI between 0 and 15 was 3.2% for women in premenopause and 9.7% for women in postmenopause, and the prevalence of a more severe SDB (AHI ≥ 15) was 0.6% and 2.7%, for premenopausal and postmenopausal women, respectively [36].

Another previous study from our group found that 50% of women in postmenopause complain of insomnia and had apnea during polysomnography recordings [37]. Guilleminault et al. [38] observed 80% of apnea subjects among postmenopausal women with insomnia.

We must state that although there are differences in some clinical aspects, including bone and climacteric symptoms, such as the number of hot flashes per day when comparing early and late postmenopausal groups, sleep pattern does not seem to be different in this comparison [39]. Our results showed that an independent effect of hot flashes was observed only in sleep latency, as women with hot flashes had increased sleep latency. Regarding the comparison between early and late postmenopausal stage, an independent effect of hot flashes was only observed in the total sleep time of the postmenopausal women as those in the late postmenopausal stage had reduced total sleep time compared to those in the early postmenopausal stage. No interaction between postmenopausal stage and hot flashes were found. Previous studies have correlated hot flashes with increased sleep fragmentation [40]. Other studies have found no evidence that hot flashes produce sleep disturbance in symptomatic postmenopausal women [41].

After controlling for age, body mass index, systolic blood pressure, diastolic blood pressure, neck, waist and hip circumference, sleep parameters such as TST (%), SL, microarousal, arousal, WASO, AHI and minimum, mean and basal SaO_2 (%), some variables that were significantly different between groups became the same. In these cases, the parameters (TST, SL, microarousal, arousal, WASO) were probably different between groups due to age.

Within the postmenopausal women, in the unadjusted analysis we found that early postmenopause women spent more time in N3 stage (%) and experienced less AHI, PLM and arousal index

Table 5
Comparison of objective sleep patterns between early and late postmenopausal women in adjusted analysis for age, body mass index, systolic blood pressure, diastolic blood pressure, neck, waist and hip circumference in EPISONO.

	Early ($n = 53$)			Late ($n = 118$)			*P* value
	Mean	SD	95% CI	Mean	SD	95% CI	
Sleep latency (min)	21.2	25.3	14.3–28.0	17.6	22.9	13.5–21.8	NS
REM sleep latency (min)[a]	130.0	76.9	109.1–150.9	106.7	69.6	94.0–119.3	NS
Total sleep time (min)	310.8	78.4	289.5–332.0	328.1	71.0	315.2–341.0	NS
Sleep efficicency (%)	75.4	13.7	71.7–79.1	78.9	12.4	76.7–81.2	NS
Stage N1 (%)	4.8	3.8	3.8–5.9	4.7	3.4	4.1–5.3	NS
Stage N2 (%)	53.6	12.2	50.3–56.9	54.9	11.0	52.9–56.9	NS
Stage N3 (%)	24.6	10.8	21.6–27.5	22.3	9.8	20.5–24.0	NS
REM sleep (%)	17.0	7.5	15.0–19.0	18.1	6.8	16.9–19.4	NS
Arousal index (number/h)	15.1	13.1	11.5–18.6	17.4	11.8	15.2–19.5	NS
Microarousal (number)	50.2	72.5	30.5–69.9	61.6	65.7	49.6–73.5	NS
WASO (min)	82.0	53.2	67.5–96.4	72.0	48.2	63.2–80.8	NS
PLM index (PLM/h)	0.4	7.8	−1.7–2.5	2.1	7.1	0.9–3.4	NS
AHI	11.4	17.7	6.6–16.2	13.0	16.1	10.1–15.9	NS
Basal SaO_2 (%)	95.0	1.8	94.5–95.5	94.9	1.6	94.6–95.2	NS
Mean SaO_2 (%)	93.7	2.1	93.2–94.3	93.9	1.9	93.6–94.3	NS
Minimum SaO_2 (%)	85.4	7.4	83.4–87.4	83.8	6.7	82.6–85.0	NS

SD: standard deviation; CI: confidence interval; NS: not significant; REM: rapid eye movement; WASO: wake after sleep onset; PLM: periodic leg movements index (number/h); AHI: apnea-hypopnea index (number/h); SaO_2: oxygen saturation level.

[a] Exception on sample size, due to missing date: REM sleep latency: early postmenopause $n = 52$ and late postmenopause $n = 115$. *P* values acquired through ANCOVA.

when compared to late postmenopausal women, indicating that the late stage was more associated with the mentioned sleep parameters. No significant differences appeared in the sleep pattern of the women in the early and late postmenopausal groups when controlled for confounders such as age. This finding is in accordance with another previous study from our group, with another population, where we found no differences between early and late postmenopausal stages, even when groups had no differences in age [42]. A cross-sectional study from Shaver et al. [43] investigated the association between sleep patterns and menopausal status and also found no significant differences between the groups.

We observed that within the 40–50 age groups there were a balanced number of women in the premenopausal and postmenopausal stage. Our results showed that menopause has an impact on sleep independent of age.

This finding is in accordance with a systematic review and meta-analysis published recently [44]. In this study authors concluded that the prevalence of sleep disturbance is higher in perimenopausal, postmenopausal, and surgical menopausal women than in premenopausal women. They also stated that there is a relationship between menopausal stages and sleep disturbance but the magnitude of the relationship is small [44].

Our study has a limitation: the volunteers did not perform a polysomnography adaptation night in order to reduce stress and get used to the environment of the exam. This may have generated a bias, as sleep architecture can be altered by stress, being monitored during sleep and by the sleep environment.

5. Conclusions

Menopause has an impact on sleep independent of age. Although modest, the effect of menopause occurs on sleep patterns as well as on sleep parameters (*i.e.*, AHI and SaO_2). There is an association between menopausal status and sleep, being worse in the postmenopausal stage relative to premenopausal stage. Even though aging is associated with differences in sleep pattern, the influence of menopause should also be taken into account by clinicians when evaluating sleep pattern in women in order to make a proper diagnosis and provide appropriate treatment.

Contributors

HH, MLA, LB and ST were responsible for the study concept. HH and LB performed the experiments. CH, CF, GNP, AGB analyzed the data. CF, AGB, HH, MLA drafted the manuscript. All authors critically reviewed content and approved the final version for publication.

Competing interests

The authors have no competing interests to declare.

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Ethical approval

The study protocol was approved by the Ethics Committee (CEP 0593/06) and registered with ClinicalTrials.gov (Identifier NCT00596713).

Conflict of interest statement

The authors have no conflict of interests to declare.

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